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Congenital anomalies of digits – a clinical-epidemiological study of 301 patients

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Abstract

Introduction: Congenital anomalies of digits (CAD) can occur as isolated malformations, in combination with other malformation of the limbs, or as part of a genetic syndrome. The purpose of this work is to provide an overview of CAD, on morphological, genetic and epidemiological basis. *Patients and Methods*: We conducted a retrospective analysis of a cohort of 301 patients with CAD. Following the Swanson classification, the list of anomalies under study included: adactyly and oligodactyly, syndactyly and symphalangism, polydactyly, macrodactyly, amniotic bands syndrome, and generalized skeletal anomalies. *Results*: In Bihor County, Romania, the Department of Medical Genetics recorded 4916 patients with congenital anomalies (2.03% out of 241 601 live newborns) between 1984 and 2018. Of these, 301 (6.1%) patients had CAD. The prevalence of CAD was 1:800 living newborns. The most common CAD were polydactyly, followed by syndactyly, brachydactyly, adactyly and oligodactyly. Upper extremities were four times more frequently affected than lower extremities, while both upper and lower extremities were affected in a quarter of all cases. CAD were isolated in 64% of patients, while 14% were associated with other anomalies of the extremities and 22% were associated with recognized genetic syndromes. *Conclusions*: Our study, by its size and the long period of clinical observation, provides opportunities to generalize and compare our data with similar studies, offering the possibility for improved knowledge of the epidemiology of CAD and potential improvements in genetic counseling.

Keywords: congenital digit anomalies, epidemiology, birth prevalence.

Introduction

The occurrence of digit anomalies in humans has attracted general interest since antiquity, capturing the curiosity of people, the imagination of the artists and the interest of ancient physicians [1]. The scientific interest has been preserved to our days due to limited explanations of the causes, of the pathogenic mechanisms and of heredity. Congenital anomalies of digits (CAD) can occur as isolated malformations, in combination with other malformations of the limbs, or as part of a syndrome. The very large diversity of minor or major CAD has generated, over time, the use of a variety of terminology and various classifications, which have often created confusion [2]. Here, we will use the standard terminology proposed by Biesecker *et al.*, in 2009 [3] and the classification proposed by Swanson and adopted by the *International Federation of Societies for Surgery of the Hand* (IFSSH) [4].

Aim

The purpose of our work is to provide an overview of CAD, on morphological, genetic and epidemiological basis.

Patients and Methods

We conducted a retrospective cohort study of patients with CAD seen in the Department of Medical Genetics of Bihor County, Romania, from 1984 to 2018. Following the Swanson classification, the list of anomalies taken into study includes: (*1*) failure of formation – adactyly, oligodactyly (including phocomelia); (*2*) failure of differentiation – syndactyly including brachysyndactyly), symphalangism; (*3*) duplication – polydactyly (including polysyndactyly); (*4*) overgrowth – macrodactyly; (*5*) undergrowth – brachydactyly; (*6*) amniotic bands syndrome; (*7*) generalized skeletal anomalies (arthrogryposis multiplex congenita). Inclusion criteria were: patients with one or more objective indubitable congenital anomalies of the fingers or toes, or both, associated or not with other anomalies of the limbs or of the different organs. The classification of CAD subtypes was mainly based on clinical criteria (local clinical examination, general clinical examination, interdisciplinary examinations – orthopedics, pediatrics surgery, physiotherapy) and radiological (bone radiographs). In the presence of association of CAD with other congenital

malformations (plurimalformative syndromes), genetic tests were performed, most commonly the karyotype from lymphocyte cultures. The following epidemiological aspects were followed and evaluated: multiannual frequency, gender distribution, family history, anatomical distribution of anomalies (upper *versus* lower extremities), left *versus* right limb, isolated finger anomalies *versus* anomalies associated with other organic malformations.

Patients with minor finger malformations or those with acquired anomalies were excluded from the study. We note here that more than 20 minor malformations of the digits are described. These should not be ignored in current practice because they may be important signs in the diagnosis algorithm of a syndrome. In the particular case of a patient with more than two different anomalies of digits, the primary defect was recorded (*e.g.*, for polysyndactyly, we considered as primary anomaly the polydactyly, while the syndactyly as a secondary one; on the contrary, for brachysyndactyly, we considered as primary anomaly the syndactyly as failure of differentiation, followed, embryologically, by brachydactyly).

Results

During the study period, we recorded 4916 patients with various congenital abnormalities (2.03% out of 241 601 live newborns). Of these, 301 (6.1%) had CAD, rendering a prevalence of CAD of 1:800 living newborns.

The multiannual frequency of CAD was relatively constant (Figure 1), with the exception of the 1986–1991 period, when we recorded a significant peak, most likely related to the Chernobyl nuclear accident that took place in 1986.

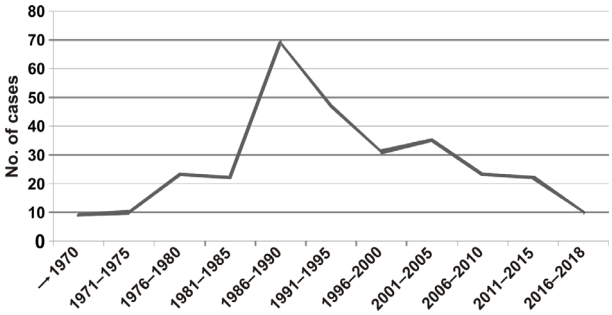

Figure 1 – ***The multiannual frequency of congenital anomalies of digits.***

There were more males affected (*n*=157; 52%) compared to females (*n*=144; 48%), but the difference was not significant.

The majority of cases of CAD appeared sporadically in the family. Of the 301 cases, 251 (83.4%) affected individuals did not have a familial history of CAD (only one case per family) while 50 (16.6%) patients belonged to only 10 families (mean of five cases per family).

The morphological types of CAD, according to the Swanson classification and location (upper *versus* lower extremities) are presented in the Table 1 and Figures 2–12. The most common CAD were polydactyly (*n*=84; 27.9%) followed by syndactyly (*n*=50; 16.6%), brachydactyly (*n*=49; 15.3%), adactyly (*n*=38; 12.6%) and oligodactyly (*n*=35; 11.6%). Upper extremity anomalies (*n*=183; 60.8%) were four times more frequent compared to lower extremity anomalies (*n*=46; 15.3%), while both the upper and lower extremities were affected in 72 (23.9%) cases.

Table 1 – ***Morphological types of CAD***

CAD (Swanson classification)		Only UE	Only LE	UE and LE	Total
Type I (failure of formation)	Adactyly*	33	1	4	38 (12.6%)
	Oligodactyly**	27	3	5	35 (11.6%
Type II (failure of differentiation)	Syndactyly	29	11	10	50 (16.6%)
	Brachysyndactyly	4	1	1	6 (2%)
	Symphalangism***	2	0	16	18 (6%)
Type III (duplication)	Polydactyly****	45	21	18	84 (27.9%)
Type IV (overgrowth)	Macrodactyly	1	4	0	5 (1.7%)
Type V (undergrowth)	Brachydactyly*****	40	5	4	49 (16.3%)
Type VI (constriction ring)	Amniotic bands syndrome	2	0	5	7 (2.3%)
Type VII (generalized skeletal anomalies)	Arthrogryposis multiplex congenita	0	0	9	9 (3%)
		183 (60.8%)	46 (15.3%)	72 (23.9%)	301 (100%)

CAD: Congenital anomalies of digits; UE: Upper extremity; LE: Lower extremity; *Associated in most cases with total or partial absence of the distal part of a limb (transverse hemimelia); **Including phocomelia; ***Including brachysymphalangism; ****Including polysyndactyly; *****Including both the short digit but with normal structure and short digit with partial absence of a digit (entire phalanx or phalangeal segment).

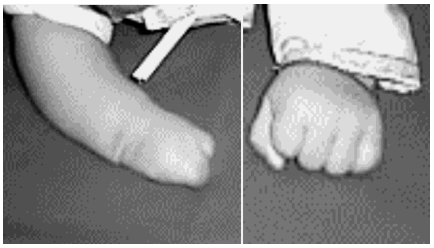

Figure 2 – ***Adactyly of right upper limb.***

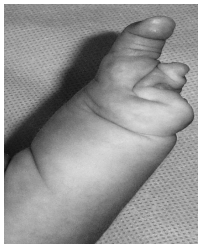

Figure 3 – ***Hand oligodactyly.***

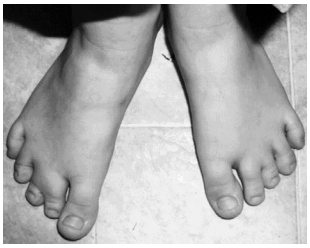

Figure 4 – ***Toes partial syndactyly.***

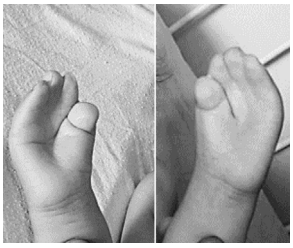

Figure 5 – ***Brachysyndactyly in Apert syndrome.***

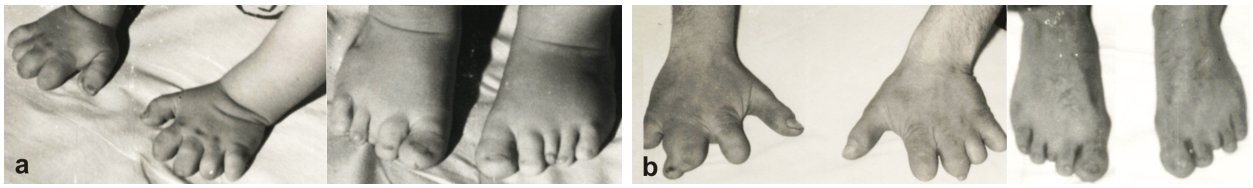

Figure 6 – ***Familial brachydactyly: Son (a) and his father (b) presenting also brachysyndactyly.***

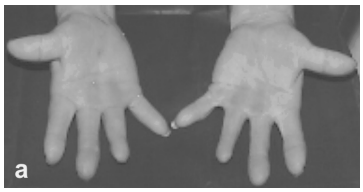

Figure 7 – ***Brachysymphalangism: (a) Brachydactyly, absence of interphalangeal groove; (b) Radiologically, the absence of interphalangeal articular space.***

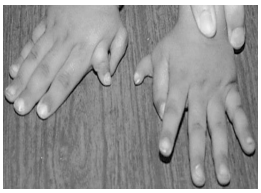

Figure 8 – ***Bilateral preaxial polydactyly in Townes–Brocks syndrome.***

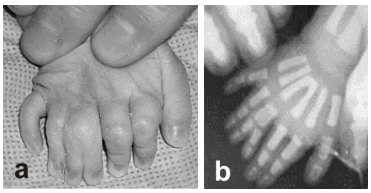

Figure 9 – ***(a and b) Bilateral mesoaxial polysyndactyly in oro-facial-digital syndrome.***

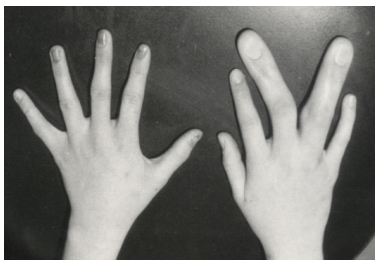

Figure 10 – ***Unilateral macrodactyly.***

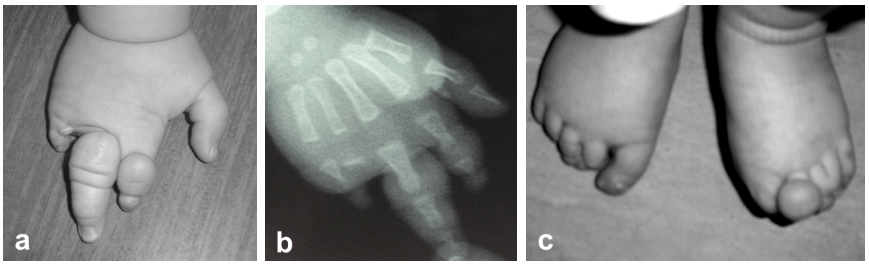

Figure 11 – ***Amniotic band syndrome: Hand and foot constriction ring (a and c); Hand oligodactyly (a) with radiological image (b).***

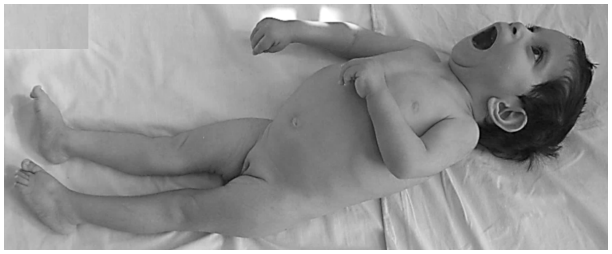

Figure 12 – ***Arthrogryposis multiplex congenita.***

There were no significant differences in the right *versus* left side distribution of CAD (Figure 13).

CAD were isolated in 64% (n=192) of patients, while 14% (n=42) were associated with other anomalies of the limbs and 22% (n=67) were associated with recognized genetic syndromes (Figure 14).

Etiologies of CAD (Figure 15) can be classified into genetic causes (n=153; 50.8%), environmental causes (n=61; 20.3%) and sporadic (unknown) causes (n=87; 28.9%).

As seen in Table 2, brachydactyly was the most common syndromic CAD (n=39; 58.2%), followed by symphalangism (n=13; 19.4%), oligodactyly (n=11; 16.4%), polydactyly (n=10; 14.9%) and syndactyly (n=9; 13.4%).

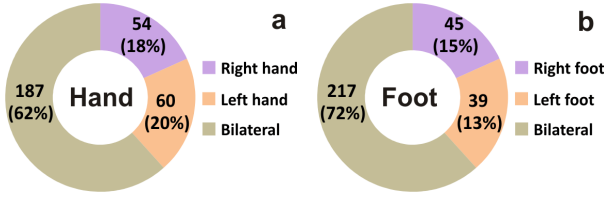

Figure 13 – ***(a and b) The right/left side distribution of congenital anomalies of digits.***

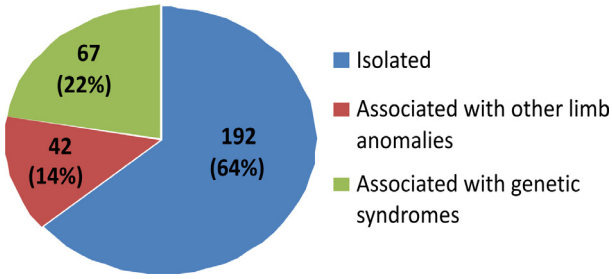

Figure 14 – ***Distribution of congenital anomalies of digits (isolated versus associated with other limb anomalies or genetic syndromes).***

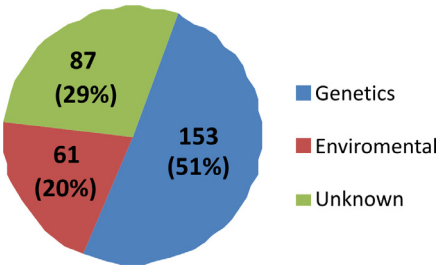

Figure 15 – ***Causes of congenital anomalies of digits.***

We have noted variable expressivity of digital anomalies both for isolated and syndromic abnormalities; the same type of anomaly can be manifested differently in terms of malformed digit(s), number of affected digits, location (upper or lower extremity, right or left) and dysfunction. This is illustrated in Figure 16, representing the pedigree of a family with brachydactyly–symphalangism–deafness syndrome [Online Mendelian Inheritance in Man (OMIM) 186500].

Table 2 – *Syndromes associated with CAD*

Syndrome	CAD	No. of cases	OMIM
Brachydactyly–symphalangism–deafness syndrome	Symphalangism, brachydactyly	13	185800
Achondroplasia	Brachydactyly	8	100800
Amniotic bands	Oligodactyly	7	217100
Hypochondroplasia	Brachydactyly	6	146000
Bardet–Biedl syndrome	Postaxial polydactyly	5	209900
Poland syndrome	Brachydactyly	4	173800
Trisomy 18	Syndactyly	3	
Rubinstein–Taybi syndrome	Brachydactyly, syndactyly	3	180849
Oro-facial-digital syndrome type I	Postaxial polydactyly	2	311200
Cornelia de Lange syndrome	Oligodactyly	2	122470
Apert syndrome	Syndactyly	2	101200
Trisomy 13	Postaxial polydactyly	1	
Down syndrome	Brachydactyly	1	
Prader–Willi syndrome	Brachydactyly	1	176270
Oro-facial-digital syndrome type VI	Central polydactyly	1	277170
Klippel–Trenaunay syndrome	Macrodactyly	1	149000
Jacobsen syndrome	Brachydactyly	1	147791
Goltz syndrome	Oligodactyly	1	305600
VACTERL association	Polydactyly	1	192350
Aarskog syndrome	Brachydactyly	1	305400
Fanconi pancytopenia	Oligodactyly	1	227650
Fraser syndrome	Syndactyly	1	219000
Holt–Oram syndrome	Brachydactyly	1	142900

CAD: Congenital anomalies of digits; OMIM: Online Mendelian Inheritance in Man; VACTERL: Vertebral anomalies–Anorectal malformations–Cardiovascular anomalies–Tracheoesophageal fistula–Esophageal atresia–Renal (kidney) and/or radial anomalies–Limb defects.

Total	67
Subtotal	83
Brachydactyly	39
Symphalangism	13
Oligodactyly	11
Polydactyly	10
Syndactyly	9
Macrodactyly	1

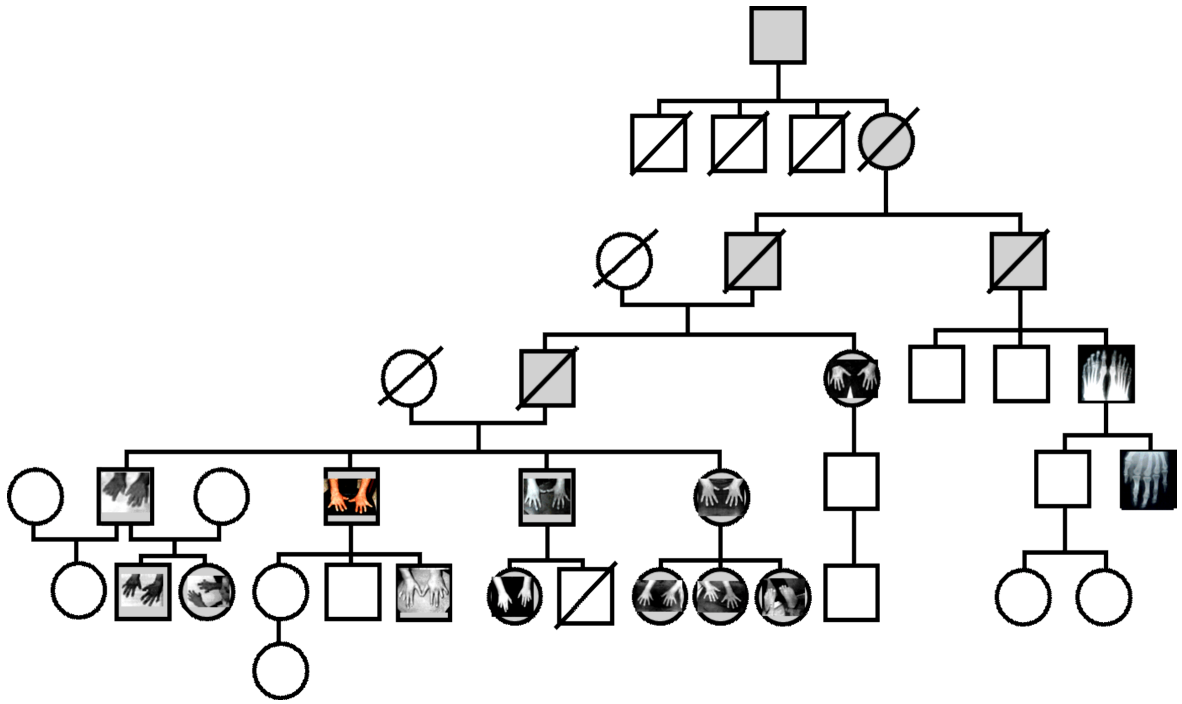

Figure 16 – *Brachydactyly–symphalangism–deafness syndrome: family tree.*

Discussions

CAD is a group of malformations with various embryonic development mechanisms, phenotypic diversity and psychosocial impact. Their study deserves distinct attention from that of the limbs. The incidence of CAD is difficult to establish and compare with other studies because different epidemiological studies have used different classifications or terminology, or have been cross-sectional studies involving a study group at a given age (*e.g.*, newborn, small children, or teenagers) [5–7]. Our study cohort included children of all ages referred to the county single Genetics Service by neonatologists (most frequently), but also by family physicians, pediatricians, rehabilitation surgeons, orthopedists, and others. However, patient referrals to the Genetics Service were likely not consistent, as reflected in the low prevalence (1:800 newborns), compared to other studies that found prevalence values of 1:300–1:500 CAD [8].

The multiannual incidence was relatively constant, except for the period between 1986 and 1991, when there was a significant increase in the number of CAD cases. This increase could be explained by two phenomena: the first would be the nuclear accident at Chernobyl (1986), even if officially not recognized to have affected our geographical area; the second could be one of Romania's demographic policies at that time, when there were severe laws forbidding the interruption of pregnancies.

The differences between right and left side were not significant, but bilateral anomalies were more frequent in the lower extremities compared to the upper extremities. At the same time, CAD were more frequently localized in the upper extremities, although genetic and embryological mechanisms do not explain this predilection for the upper limbs. A subjective error factor could be taken into account because upper extremity abnormalities are "more visible" and the upper extremities are considered "more useful", likely leading to higher rates of patient referrals to specialized services.

The criteria to classify an anomaly as having a genetic cause were: positive familial history, affecting both the upper and the lower extremities or both the right and the left side, association with known syndromes, association with other major congenital anomalies, uneventful history of pregnancy.

Genetic causes of CAD are beginning to become better and better known [9, 10]. There are more than 100 genes implicated in the morphogenesis of the limbs and more than 100 recognized syndromes with hand anomalies, as a part of their expression [11–13].

Family history is an important criterion for defining the hereditary pattern of CAD. In our study, family history was positive in 50 of the 301 (16.6%) cases; 31 of affected individuals had isolated finger abnormalities and 19 cases presented with different genetic syndromes [14–17]. Intra-familial clustering could be explained either by deprivation of genetic counseling, or by accepting the risk, implicitly by destiny.

Brachydactyly is the most common digital anomaly associated with syndromes. This is the reason why we believe that this sign must be searched and objectively confirmed by rigorous somatometry in each case. Brachydactyly is defined as shortening of the middle finger of the hand of more than two standard deviations below the mean in newborns with of 27 to 41 weeks gestation, and less than the third percentile for age in infants and children up to 16 years. Isolated finger abnormalities in patients with negative family history may be the consequence of a *de novo* mutation or environmental factors [18].

The scientific interest of this study must also be understood through the consequences of this pathology on the psychological, social and economic level.

Conclusions

Our study, by its size and the long period of clinical observation, offers opportunities to generalize and compare our data with similar studies, improving knowledge of causes and performance of genetic counseling. By frequency, severity and psychosocial implications, CAD are an important group of congenital anomalies, with major impact on patients and their families.

Ethical Approval

The study was approved by the Ethics Committee of "Dr. Gavril Curteanu" Municipal Hospital, Oradea, Romania.

Conflict of interests

All authors declare no conflict of interests.

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